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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,173	06/24/2004	Katsuhito Takahashi	4439-4022	3299

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EXAMINER

RIGGINS, PATRICK S

ART UNIT PAPER NUMBER

1633

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/500,173

Applicant(s)

TAKAHASHI ET AL.

Examiner

Patrick S. Riggins

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 June 2004.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-7 is/are rejected.
7) ☒ Claim(s) 8-36 is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 24 June 2004 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 6/24/04.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Presently claims 1-36, filed as a National stage entry of PCT/JP02/13683 on 6/24/04, are pending and under examination.

Drawings

2. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the drawings, particularly the images are all too dark to allow one to see the data that is presented. Applicant is advised to employ the services of a competent patent draftsman outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

4. The abstract exceeds the 150 word limit. Further the abstract should be replaced, as it is in non-idiomatic English.

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5. A substitute specification in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) is required. The substitute specification filed must be accompanied by a statement that it contains no new matter.

6. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
- (f) BACKGROUND OF THE INVENTION.
 - (1) Field of the Invention.
 - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

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The headings that are presently in the specification do not properly separate the sections. For example, the background and summary of the invention are grouped into a single section.

Claim Objections

7. Claims 8-36 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

8. Claims 1-7 are objected to because of the following informalities: the claims are presented in non-idiomatic English and as such the scope of the claims is difficult to ascertain. For example, the phrase “to adult normal cells” is not art-recognized and is wholly unclear. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. The claims are drawn to “a cell-specific” vector. As any vector which can lead to the expression of a protein in a cell is indeed “cell-specific”, it is unclear what is intended by this limitation in the claims. Indeed it would appear that applicants intend that the vector will replicate and express its gene of interest in a *specific* cell type, but the claims make no such

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requirement of any particular cell specificity. Is this limitation meant to indicate that the vector is tumor cell specific or smooth muscle cell specific or specific for some other undefined cell type?

Without proper indication what sort of cell-specificity is intended, the skilled artisan would be unable to ascertain the metes and bounds of this limitation in the claims.

12. The claims all recite that the vector “does not act to adult normal cells”. This is vague and indefinite because it is unclear what is intended by the limitation or even how one would “adult” cells. A basic interpretation could be that “adult” is roughly equivalent to differentiate, but this is further vague and indefinite because normal adult cells are indeed already differentiated. Thus, the skilled artisan would be unable to ascertain the metes and bounds of this limitation in the claims. Further it is unclear what is intended by “a predetermined gene”.

13. Claim 1 recites that the vector “is used to suppress the replication at a desired period”. Does this mean the vector will not replicate or the cell into which the vector has been introduced will not replicate?

14. Based upon the sequence listing, it is clear that SEQ ID NO: 1 is a portion of SEQ ID NO: 2, which is a portion of SEQ ID NO: 3. Upon reading claims 2-4 however one can easily come to the conclusion that SEQ ID NO: 1 is the largest of the fragments. As such the wording of these claims is unclear and the skilled artisan would have great difficulty in determining the metes and bounds of these claims.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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16. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an HSV vector comprising SEQ ID NO: 3 operably linked to an ICP4 gene and a TK gene, does not reasonably provide enablement for any other vector comprising SEQ ID NO: 1, SEQ ID NO: 2, or any variant with an unspecified number of deletions, substitutions, or additions to SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

17. When considering whether the specification in view of the prior art enables the skilled artisan to practice the claimed invention without undue levels of experimentation, a number of factors are considered in making this determination as delineated by *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

18. The claims embrace any vector comprising a tissue specific promoter that can be SEQ ID NO: 1, 2, or 3 that controls the expression of a gene essential for viral replication and a thymidine kinase (TK) gene. Although SEQ ID NOs: 1 and 2 are indeed portions of SEQ ID NO: 3, and SEQ ID NO: 1 has been specifically shown to be necessary for the tissue specificity of the calponin promoter, there has been no showing that neither of SEQ ID NOs: 1 or 2 is sufficient to grant the tissue specificity of the calponin promoter. This region consisting of SEQ ID NO: 3, identified as -260 to +73 of the human calponin gene, was identified through a series of 5'

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truncations of the calponin upstream regulatory sequence. Tissue-specific promoter activity was lost upon truncation from -260 to -239. Indeed SEQ ID NO: 1 is this region from -260 to -239 (for this truncation data see Figure 1 of Yamamura; Cancer Res 61: 3969-3977 (2001), of record). Indeed this data establishes that SEQ ID NO: 1 is necessary for tissue-specific promoter activity of the calponin promoter, it in no way establishes that either SEQ ID NO: 1 or SEQ ID NO: 2 is sufficient for this activity. In full support of this, the specification at the paragraph bridging pages 34 and 35 clearly identifies SEQ ID NO: 3 as the required minimal region: "The minimum expression regulation region (-260 to +73) was identified by the method described previously". Thus, by applicants' own admission, SEQ ID NO: 3 is the minimal domain required to achieve the tissue specificity granted by the calponin promoter. The specification offers no evidence that either of SEQ ID NO: 1 or SEQ ID NO: 2 could act in the tissue specific manner desired, and the specification offers no guidance regarding any functional variants of SEQ ID NO: 3 that have any substitutions, deletions, or additions or any other form of vector aside from an HSV vector. There is no guidance regarding any structural or sequence requirements or functional domains required to give at least minimal activity of the cell-specific promoter.

19. Therefore in order to make any vector comprising only SEQ ID NO: 1, SEQ ID NO: 2 or any variant of SEQ ID NO: 3, the skilled artisan would be required to fully characterize the activity of these vectors, and indeed identify any additional sequences that may be required in order to achieve functional expression of a gene of interest in a tissue specific manner if one were to start with only SEQ ID NO: 1 or SEQ ID NO: 2. Clearly any experimentation of this nature would be of the trial and error type, as the specification offers no guidance in this regard. Indeed, the specification itself states that SEQ ID NO: 3 is indeed the minimal domain required.

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Thus, to make and use any vector for tissue-specific expression comprising only SEQ ID NO: 1, SEQ ID NO: 2, or any variant of SEQ ID NO: 3, the skilled artisan would be required to perform an undue level of experimentation.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,728,379 (hereinafter Martuza, newly cited).

22. Claim 1 is broadly drawn to any vector with a cell-specific promoter presumable driving expression of a gene, with the vector further comprising a TK gene. Claim 6 places an enhancer upstream of the cell-specific promoter.

23. Martuza discloses and claims an HSV vector with a functional TK where a tissue-specific promoter controls the expression of for example the ICP4 gene (see column 25, lines 39-62; column 29; column 33, lines 48-64; the claims, and Figures 4-7). Further Martuza also discloses tissue-specific enhancers upstream of the promoter (see for example Figure 1 and its Brief description at column 6, lines 42-45). Thus Martuza anticipates a vector as claimed in claims 1 and 6.

Claim Rejections - 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

25. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza as applied to claims 1 and 6 above under 35 U.S.C. 102(b), and further in view of Yamamura (Cancer Res 61: 3969-3977 (5/2001), of record).

26. Martuza discloses a vector as described above meeting the limitations of claim 1. Martuza does not disclose the specific sequences as the tissue-specific promoter of the calponin gene, defined as SEQ ID NO:1, SEQ ID NO: 2, or SEQ ID NO: 3. Martuza further does not disclose the 4F2 enhancer upstream of the tissue-specific promoter.

27. Yamamura discloses vectors comprising the cell-specific HSV vectors comprising residues -260 to +73 of the human calponin promoter, which is SEQ ID NO: 3 and comprises both SEQ ID NO: 2 and SEQ ID NO: 1, driving the expression of the ICP4 gene (see page 3970, column 1, fourth full paragraph and Figure 1A). Yamamura further discloses a vector where the 4F2 enhancer is upstream of SEQ ID NO: 3 to further upregulate expression of ICP4 (see Figure 1B, and page 3972, column 1, first paragraph). The vectors of Yamamura disrupt the TK gene and thus do not contain a functional TK gene, however Yamamura indeed discloses that vectors were being constructed that included an intact TK gene for sensitivity of the cells to acyclovir and gancyclovir (see page 3976, column 1, first paragraph).

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28. One would have been motivated to use the 4F2 enhancer and -260 to +73 of the calponin promoter in the TK expressing vectors of Martuza because Martuza teaches that “such a vector would be hypersensitive to gancyclovir” (column 25, line 55). One would have had a reasonable expectation of success because Yamamura expresses a clear desire to make exactly this vector which would have “improve efficacy and safety for preclinical and clinical testing (page 3976, column 1, first paragraph). It would therefore have been *prima facie* obvious to one of ordinary skill in the art to use the promoter and enhancer taught by Yamamura in the vectors taught by Martuza.

29. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. 2004/0197308 (hereinafter Takahashi) in view of Martuza (U.S. Patent No. 5,728,379) and Yamamura (Cancer Res 61: 3969-3977 (5/2001), of record).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention “by another”; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in

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accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

30. Takahashi discloses the identical mapping of the calponin promoter as the instant invention. Indeed reference claims 1-7 are essentially identical to instant claims 1-7 with the exception that the reference claims are not limited such that the vector further comprises a thymidine kinase gene.

31. Martuza discloses HSV vectors for use in the specific killing of tumor cells through the use of tissue specific promoters. Indeed, Martuza teaches of the advantages of using a vector wherein the TK gene is intact and thus cell killing could be induced by treatment with gancyclovir (see above, and column 25, lines 39-62). One would have been motivated to include a functional TK gene, as taught by Martuza, in the vectors of Takahashi because Martuza specifically teaches the benefits of using a cell-specific promoter to drive expression of an ICP4 gene in a vector with an intact TK gene (see column 25, lines 39-62; column 29; column 33, lines 48-64; the claims, and Figures 4-7). Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to include an intact TK gene, as taught by Martuza, in the calponin promoter vectors of Takahashi, with a reasonable expectation of success because Yamamura, which discloses the same mapping data as Takahashi, clearly indicates that inclusion of an intact TK gene is a desired embodiment which would “improve efficacy and safety for preclinical and clinical testing (Yamamura, page 3976, column 1, first paragraph).

Double Patenting

32. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

33. Claims 1-7 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, respectively, of copending Application No. 10/477,797 in view of Martuza (U.S. Patent No. 5,728,379) and Yamamura (Cancer Res 61: 3969-3977 (5/2001), of record).

34. The reference claims teach identical vectors to those claimed in the instant application with the exception that the vectors of the reference claims do not include a TK gene in the vector. Indeed the definition provided in the specification regarding embodiments of the vector clearly includes HSV vectors. In fact, the exemplification throughout the reference specification is with HSV-based vectors.

35. Martuza discloses HSV vectors for use in the specific killing of tumor cells through the use of tissue specific promoters. Indeed, Martuza teaches of the advantages of using a vector

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wherein the TK gene is intact and thus cell killing could be induced by treatment with gancyclovir (see above, and column 25, lines 39-62). One would have been motivated to include a functional TK gene, as taught by Martuza, in the vectors of the reference claims because Martuza specifically teaches the benefits of using a cell-specific promoter to drive expression of an ICP4 gene in a vector with an intact TK gene (see column 25, lines 39-62; column 29; column 33, lines 48-64; the claims, and Figures 4-7). Therefore it would have been obvious to one of ordinary skill in the art to include an intact TK gene, as taught by Martuza, in the vectors claimed in 10/477,797, with a reasonable expectation of success because Yamamura, which discloses the same mapping data as claimed in the reference application, clearly indicates that inclusion of an intact TK gene is a desired embodiment which would “improve efficacy and safety for preclinical and clinical testing (Yamamura, page 3976, column 1, first paragraph).

This is a provisional obviousness-type double patenting rejection.

Conclusion

36. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
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ANNE M. WEHBE PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'A. Wehbe', with a long horizontal line extending to the right.